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10/786,223	02/23/2004	Thomas Maciag	536895013CT1	3032

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EXAMINER	
WOODWARD, CHERIE MICHELLE	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,223	MACIAG ET AL.	
	Examiner	Art Unit	
	CHERIE M. WOODWARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's Response and amendments, filed 14 March 2008, is acknowledged and entered. Applicant's substitute specification is acknowledged and entered. Claims 1-20 are pending. Claims 1-5 and 14-20 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 6-13 are under examination.

Response to Arguments

Claim Rejections Withdrawn

2. The rejection of claims 7-13 under 35 U.S.C. 103(a) as being unpatentable over Brewer et al., WO 200013712 (published 16 March 2000), Wang et al., (Biochem. Biophys. Res. Commun. 2000 271:138-143), and Wempe et al., (Arterioscler Thromb Vasc Biol. 1997 Nov;17(11):2471-8), is withdrawn in light of Applicant's argument. However, a new rejection is set forth below, as being necessitated by Amendment.

Claim Rejections Maintained

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claim 6 remains rejected under 35 U.S.C. 102(b) as being anticipated by Applebaum et al., (Free Radic Biol Med. 1990;8(2):133-43) (abstract only), for the reasons of record and the reasons set forth herein.

Applicant argues that an inherency argument is not as applicable to method claims as it is to composition claims (Remarks, page 7, second paragraph). Applicant argues that the methods taught by Applebaum et al., cannot anticipate a method of inhibiting neointima formation where the method comprises inhibiting IL-1α release from a cell (Remarks, p. 7, last paragraph to p. 8, first paragraph). Applicant argues that in order to anticipate the claimed invention, Applebaum must describe the method of neointima formation (Remarks, p. 8, second paragraph). Applicant argues that Applebaum et al., does

not disclose the element of IL-1α release, a method of inhibiting IL-1α release from a cell, or the use of a copper chelator to inhibit IL-1α release from a cell (Remarks, p. 8, last paragraph). Applicant also argues that the specification states that the claimed effect on IL-1α release from a cell is not inherent in the mere chelation of copper (Remarks, p. 8, last paragraph). Applicant argues that the key to the present invention is preventing the formation of a multimolecular aggregate required for IL-1α release from a cell (Remarks, p. 8, last paragraph). Applicant's arguments have been fully considered but they are not persuasive.

With regard to Applicant's argument that inherency law is not as applicable to method claims as it is to composition claims (Remarks, page 7, second paragraph), Applicant is directed to In re Tomlinson, 363 F.2d 928, 150 USPQ 623 (CCPA 1966) (stating that the claim was directed to a process of inhibiting light degradation of polypropylene by mixing it with one of a genus of compounds, including nickel dithiocarbamate. A reference taught mixing polypropylene with nickel dithiocarbamate to lower heat degradation. The court held that the claims read on the obvious process of mixing polypropylene with the nickel dithiocarbamate and that the preamble of the claim was merely directed to the result of mixing the two materials. "While the references do not show a specific recognition of that result, its discovery by appellants is tantamount only to finding a property in the old composition." 363 F.2d at 934, 150 USPQ at 628 (emphasis in original).). Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986) (The claims were directed to a method of enhancing color effects produced by ambient light through a process of absorption and reflection of the light off a coated substrate. A prior art reference to Donley disclosed a glass substrate coated with silver and metal oxide 200-800 angstroms thick. While Donley disclosed using the coated substrate to produce architectural colors, the absorption and reflection mechanisms of the claimed process were not disclosed. However, King's specification disclosed using a coated substrate of Donley's structure for use in his process. The Federal Circuit upheld the Board's finding that "Donley inherently performs the function disclosed in the method claims on appeal when that device is used in normal and usual operation'" and found that a prima facie case of anticipation was made out. Id. at 138, 801 F.2d at 1326. It was up to applicant to prove that Donley's structure would not perform the claimed method when placed in ambient light.). See also In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) (Applicant claimed a process for preparing a hydrolytically-stable zeolitic aluminosilicate

which included a step of "cooling the steam zeolite ... at a rate sufficiently rapid that the cooled zeolite exhibits a X-ray diffraction pattern ...." All the process limitations were expressly disclosed by a U.S. patent to Hansford except the cooling step. The court stated that any sample of Hansford's zeolite would necessarily be cooled to facilitate subsequent handling. Therefore, a prima facie case under 35 U.S.C. 102 /103 was made. Applicant had failed to introduce any evidence comparing X-ray diffraction patterns showing a difference in cooling rate between the claimed process and that of Hansford or any data showing that the process of Hansford would result in a product with a different X-ray diffraction. Either type of evidence would have rebutted the prima facie case under 35 U.S.C. 102. A further analysis would be necessary to determine if the process was unobvious under 35 U.S.C. 103.); Ex parte Novitski, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.).

In response to applicant's arguments, the recitation "[a] method of inhibiting neointima formation" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). The phrase "thereby inhibiting said neointima formation" in the body of the claim is an intended purpose of the claimed process, but the process steps are drawn only to administering an amount of a copper chelator in an amount sufficient to inhibit IL-1α release, wherein the IL-1α release is non-traditional IL-1α release. It is understood that the claim preamble must be read in the context of the entire claim. The determination of whether preamble recitations are structural limitations or mere statements of purpose or use "can be resolved only on review of the entirety of the [record] to gain an understanding of what the inventors actually invented and intended to encompass by the claim." Corning Glass Works, 868 F.2d at 1257, 9 USPQ2d at 1966. If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's

limitations, then the preamble is not considered a limitation and is of no significance to claim construction. Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also Rowe v. Dror, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir.1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation"); Kropa v. Robie, 187 F.2d at 152, 88 USPQ2d at 480-81 (preamble is not a limitation where claim is directed to a product and the preamble merely recites a property inherent in an old product defined by the remainder of the claim); STX LLC. v. Brine, 211 F.3d 588, 591, 54 USPQ2d 1347, 1350 (Fed. Cir. 2000) (holding that the preamble phrase "which provides improved playing and handling characteristics" in a claim drawn to a head for a lacrosse stick was not a claim limitation). Compare Jansen v. Rexall Sundown, Inc., 342 F.3d 1329, 1333-34, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003) (In a claim directed to a method of treating or preventing pernicious anemia in humans by administering a certain vitamin preparation to "a human in need thereof," the court held that the preamble is not merely a statement of effect that may or may not be desired or appreciated, but rather is a statement of the intentional purpose for which the method must be performed. Thus the claim is properly interpreted to mean that the vitamin preparation must be administered to a human with a recognized need to treat or prevent pernicious anemia.); In re Cruciferous Sprout Litig., 301 F.3d 1343, 1346-48, 64 USPQ2d 1202, 1204-05 (Fed. Cir. 2002) (A claim at issue was directed to a method of preparing a food rich in glucosinolates wherein cruciferous sprouts are harvested prior to the 2-leaf stage. The court held that the preamble phrase "rich in glucosinolates" helps define the claimed invention, as evidenced by the specification and prosecution history, and thus is a limitation of the claim (although the claim was anticipated by prior art that produced sprouts inherently "rich in glucosinolates")). In the instant case, the preamble is in accord with at least Jansen v. Rexall Sundown, Inc., and In re Cruciferous Sprout Litig., because the preamble does not limit process steps of the claim. Instead, it merely explains the purpose of what a specific amount of a copper chelator is intended to do. In light of the facts and the law in this area, Applebaum does not need to the method of neointima formation nor disclose the element of IL-1α release, a method of inhibiting IL-1α release from a cell, or the use of a copper chelator to inhibit IL-1α release from a cell in order to anticipate the instant claim.

Regarding Applicant's argument that the key to the present invention is preventing the formation of a multimolecular aggregate required for IL-1α release from a cell (Remarks, p. 8, last paragraph), this is an intended purpose of the administration. The examiner previously explained in the Office Action of 10/22/2007 that the discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. In re Hack, 245 F.2d 246, 248, 114

USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978). In the instant case, because the Applebaum reference teaches the administration of a copper chelator to the same population (mammals with vessel injury) the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) has no bearing on patentability, particularly in light of the fact that Applebaum et al., teaches neocuproine at the range of 40-175 μM provided protection at the level of 70-85%, as demonstrated by the reduced loss in the peak systolic pressure (P), in +dP/dt and in -dP/dt.

5. Claims 6, 9, and 11-13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Brewer et al., WO 200013712 (published 16 March 2000), for the reasons of record and the reasons set forth herein.

Applicant argues that Brewer cannot anticipate the presently claimed invention because Brewer does not disclose the claimed element of inhibiting IL-1α release from a cell or the use of a copper chelator to inhibit IL-1α release from a cell, a method to prevent neointima formation following vessel injury, cell proliferation associated with arterial wall injury, secretion of extracellular matrix following arterial wall injury, or neointimal thickening associated with arterial wall injury (Remarks, p. 9, third paragraph). Applicant argues that a method of treating neovascularization, aberrant vascularization, aberrant angiogenesis, wet type macular degeneration, or rheumatoid arthritis taught by Brewer cannot anticipate a method of inhibiting IL-1α release from a cell or the use of a copper chelator to inhibit IL-1α release from a cell for inhibiting neointima formation following vessel injury, cell proliferation associated with arterial wall injury, secretion of extracellular matrix following arterial injury, or neointimal thickening associated with arterial wall injury (Remarks, p. 9, fourth paragraph). Applicant argues that pathological neovasularization and aberrant angiogenesis are defined by the growth of new blood vessels, but neointima formation, cell proliferation, and secretion of extracellular matrix associated with arterial wall injury are all part of a blood vessel's response to injury and are involved in scar formation at the site of injury (Remarks, p. 9, last paragraph to page 10, first paragraph). Applicant argues that a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis cannot anticipate a method of inhibiting IL-1α release from a cell or the use of a copper chelator to inhibit IL-1α release from a cell to prevent neointima formation following vessel injury and the like (Remarks, p. 10, first paragraph). Applicant also argues that the specification states that the claimed effect on IL-1α release from a cell is not inherent in the mere chelation of copper because IL-1α release is also inhibited by the

truncated form of S100A13, a Ca2+ binding protein (Remarks, p. 10, second paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

As set forth in detail above, the prior art need not appreciate an unknown property of the composition. When a claim recites using an old composition or structure and the use is directed to a result or property of that composition or structure, then the claim is anticipated. In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978). In the instant case, because WO 00/13712 teaches a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis (pages 3 and 55-56), by administering the copper chelator tetrathiomolybdate (pp. 19- 25), the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) has no bearing on patentability, particularly in light of the fact that WO 00/13712 teaches administration of TTM to the same population and for the same overarching purpose, to treat neovascularization, aberrant vascularization, and aberrant angiogenesis.

With regard to Applicant's argument that neointima formation, cell proliferation, and secretion of extracellular matrix associated with arterial wall injury are all part of a blood vessel's response to injury and are involved in scar formation at the site of injury and that a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis cannot anticipate a method of inhibiting IL-1α release from a cell or the use of a copper chelator to inhibit IL-1α release from a cell to prevent neointima formation following vessel injury and the like, Applicant's attention is drawn to the previous Office Action (10/22/2007) at page 4, last paragraph, where the examiner also sets forth that Brewer et al., also teaches administering TTM in the treatment of trauma, diabetic retinopathy, macular degeneration, vein occlusion, artery occlusion, chronic inflammatory diseases, and atherosclerosis at pp. 55-57; all of which are part of a blood vessel's response to injury and are involved in scar formation at the site of injury. Brewer et al., teaches the method of administering TTM for the same purpose claimed by Applicant, even if the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) was unappreciated by Brewer et al.

Applicant's argument that the claimed effect on IL-1α release from a cell is not inherent in the mere chelation of copper because IL-1α release is also inhibited by the truncated form of S100A13, a Ca2+ binding protein, ignores the fact that the prior art also recognizes S100A13 as a Cu2+ binding protein. Applicant's attention is directed to Landriscina et al., (J Biol Chem. 2001 Jul 6;276(27):25549-57. Epub 2001 May 10) (cited for exemplary purposes only in response to Applicant's arguments). Landcrisha et al., teach that S100A13 is also able to interact in the presence of Cu2+ with Cys-free FGF1 and this observation may account for the ability of S100A13 to export Cys-free FGF1 in response to

stress (abstract). Landriscina et al., also teach that tetrathiomolybdate, a Cu2+ chelator, significantly represses in a dose-dependent manner the heat shock-induced release of FGF1 and S100A13 (abstract). Additionally, Landriscina et al., state that the data suggest that S100A13 may be involved in the assembly of the multiprotein aggregate required for the release of FGF1 and that Cu2+ oxidation may be an essential post-translational intracellular modifier of this process.

New Rejection – Necessitated by Amendment

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 6-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brewer et al., WO 200013712 (published 16 March 2000) (previously cited of record) and Wempe et al., (Arterioscler

Thromb Vasc Biol. 1997 Nov;17(11):2471-8) (previously cited of record), as evidenced by Dayer et al., (Am Rev Respir Dis. 1993 Dec;148(6 Pt 2):S70-4, Abstract Only) and Issekutz (J Immunol. 1995 Jun 15 ;154(12):6533-40).

The Examiner finds the following facts:

a. The instant claims are drawn to methods of inhibiting neointima formation, macrophage infiltration following vessel injury, cell proliferation, extracellular matrix formation following arterial wall injury, and adventitial angiogenesis associated with arterial wall injury by administering a copper chelator.

b. WO 00/13712 teaches a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis (pages 3 and 55-56), by administering the copper chelator tetrathiomolybdate (pp. 19- 25). WO 00/13712 teaches that disorders such as the "wet" type of macular degeneration occurs when abnormal new blood vessels or neovascular membranes grow from the choroid through the damaged pigment epithelium and under the macula (p. 54). These neovascular membranes are fragile and are prone to hemorrhage, which results in severe distortion of the macular tissue (p. 54). Other diseases associated with corneal neovascularization include epidemic keratoconjunctivitis, vitamin A deficiency, contact lens overwear, atopic keratitis, Sjogren's syndrome, chemical burns, bacterial ulcers, herpes simplex infections, Kaposi sarcoma, rheumatoid arthritis, systemic lupus erythmatosus, trauma, diabetic retinopathy, macular degeneration, vein occlusion, artery occlusion, chronic inflammatory diseases, and atherosclerosis (pp. 55-57). Atherosclerotic plaques formed within the lumen of blood vessels have been shown to have angiogenic stimulatory activity (p. 57, first paragraph). WO 00/13712 teaches that tetrathiomolybdate forms a stable tripartite complex with copper and protein (p. 18, line 28-29). WO 00/13712 teaches the treatment of diseases characterized by aberrant angiogenesis and neovascularization based on modulation of total-body copper status because copper is a required co-factor for the function of many key mediators of angiogenesis (p. 18, lines 4-9). WO 00/13712 teaches administration of tetrathiomolybdate in a non-anemia inducing amount of 20mg six times a day in patients with Wilson's disease (p. 22, lines 7-8). High dose ranges encompass 350-1400 mg/day (p. 22, line 18) and dose ranges of 25-50 mg day (p. 22, line 20) are taught as being well tolerated with no adverse side effects.

c. WO 00/13712 does not teach macrophage infiltration after vessel injury.

d. Wempe et al., teach macrophage infiltration after vessel injury (abstract). Preferential adhesion of monocytic cells to migrating endothelial cells is demonstrated *in vivo* after balloon denudation injury of rat aortas (p. 5 of 16, second paragraph).

e. Dayer et al., provide evidence that cell-associated IL-1α plays a crucial role in the process of cell-cell interaction between monocytes and fibroblasts and that this interaction may be controlled by inhibitors of IL-1 (abstract).

f. Issekutz provides evidence that IL-1α plays a crucial role in the process of cell-cell interaction between monocytes and endothelial cells (abstract; p. 6535, column 1, results; Figure 1).

g. The level of skill of those in the art encompasses skills in the field of molecular biology relating to administration of copper chelators to treat inflammatory responses.

h. A person of ordinary skill in the art at the time the invention was made would have reasonably known that the copper chelator tetrathiomolybdate was used for treating conditions such as trauma, inflammation, vessel injury, and inhibiting new vessel formation. Further, a person of ordinary skill in the art would have been able to inhibit neointima formation, macrophage infiltration, cell proliferation associated with arterial wall injury, secretion of extracellular matrix following arterial wall injury, and adventitial angiogenesis by using well-known methodologies and protocols, such as the ones taught by WO 00/13712.

i. Because the WO 00/13712 reference teaches administration of the same compound as the instant claims (tetrathiomolybdate) to the same population (mammals with vessel injury, inflammation, and arterial wall injury), the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) has no bearing on patentability. The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. In re Hack, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978).

In view of the facts recited above, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results. The prior art teaches all of the limitations of the claimed invention. WO 00/13712 teaches administration of tetrathiomolybdate to a population comprising mammals with

diseases characterized by aberrant angiogenesis, neovascularization, inflammation, trauma, and angiogenic stimulatory activity of atherosclerotic plaques formed within the lumen of blood vessels (compare instant claims 6, 9, 11-13). Macrophage infiltration after vessel injury is taught by Wempe et al., who demonstrate preferential adhesion of monocytic cells to the endothelial cells at the migration front *in vivo* after balloon denudation injury of rat aortas (p. 5 of 16, second paragraph) (claims 7, 8, and 10). Applicants have previously stated that "an IL-1α release inhibiting amount" is set forth in the specification at Example 2 (page 48 of the specification as originally filed) as 10mg/kg to rats (see Response, filed 12 January 2007, p. 14, second paragraph) with no adverse side effects. WO 00/13712 teaches administration of tetrathiomolybdate within this range (see above).

The person of ordinary skill in the art would have combined the elements as claimed by known methods to inhibit macrophage infiltration, wherein the macrophage infiltration is associated with inflammation, and to treat arterial wall injury following balloon angioplasty in light of the teachings of Brewer et al., and Wempe et al., showing administration of the copper chelator TTM affects neointima formation following injury, inflammation, and trauma (Brewer et al.,), as well as and monocytic cell activation and infiltration following balloon denudation injury (Wempe et al.). Because Brewer et al., teaches administration of the same compound as the instant claims (tetrathiomolybdate) (TTM) to the same population (mammals with vessel injury, inflammation, and arterial wall injury), the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) has no bearing on patentability. Wempe et al., need not appreciate the involvement of IL-1α in recruiting macrophages/monocytes after vessel injury. This is appreciated in the prior art. See, for evidentiary purposes only, Issekutz (J Immunol, 1995 Jun 15;154(12):6533-40) (abstract; p. 6535, column 1, results; Figure 1) and Dayer et al., (cited as an evidentiary reference) provide evidence that cell-associated IL-1α plays a crucial role in the process of cell-cell interaction between monocytes and fibroblasts and that this interaction may be controlled by inhibitors of IL-1. It is sufficient that Wempe et al., teach the preferential adhesion of monocytic cells to migrating endothelial cells (including fibroblasts) demonstrated *in vivo* after balloon denudation injury of rat aortas (p. 5 of 16, second paragraph). One of ordinary skill in the art would understand the role played by IL-1α in the process of cell-cell interaction between monocytes and cell types such as fibroblasts (as evidenced by Dayer et al.,) and endothelial cells (as evidenced by Issekutz).

The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. In re Hack, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the

"use" is directed to a result or property of that composition or structure, then the claim is anticipated. In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978). One of skill in the art would have recognized that the results of the combination of administering the copper chelator TTM for the claimed intended use would have would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made.

Additionally, the mechanism of the instant claims is an inherent property of the administration of the copper chelator, TTM. Brewer et al., teaches administering TTM in the treatment of trauma, diabetic retinopathy, macular degeneration, vein occlusion, artery occlusion, chronic inflammatory diseases, and atherosclerosis at pp. 55-57; all of which are part of a blood vessel's response to injury and are involved in scar formation at the site of injury. Brewer et al., teaches the method of administering TTM for the same purpose claimed by Applicant, even if the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) was unappreciated by Brewer et al. Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986) (The claims were directed to a method of enhancing color effects produced by ambient light through a process of absorption and reflection of the light off a coated substrate. A prior art reference to Donley disclosed a glass substrate coated with silver and metal oxide 200-800 angstroms thick. While Donley disclosed using the coated substrate to produce architectural colors, the absorption and reflection mechanisms of the claimed process were not disclosed. However, King's specification disclosed using a coated substrate of Donley's structure for use in his process. The Federal Circuit upheld the Board's finding that "Donley inherently performs the function disclosed in the method claims on appeal when that device is used in normal and usual operation'" and found that a prima facie case of anticipation was made out. Id. at 138, 801 F.2d at 1326. It was up to applicant to prove that Donley's structure would not perform the claimed method when placed in ambient light.). See also In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) (Applicant claimed a process for preparing a hydrolytically-stable zeolitic aluminosilicate which included a step of "cooling the steam zeolite ... at a rate sufficiently rapid that the cooled zeolite exhibits a X-ray diffraction pattern ...." All the process limitations were expressly disclosed by a U.S. patent to Hansford except the cooling step. The court stated that any sample of Hansford's zeolite would necessarily be cooled to facilitate subsequent handling. Therefore, a prima facie case under 35 U.S.C. 102 /103 was made. Applicant had failed to introduce any

evidence comparing X-ray diffraction patterns showing a difference in cooling rate between the claimed process and that of Hansford or any data showing that the process of Hansford would result in a product with a different X-ray diffraction. Either type of evidence would have rebutted the prima facie case under 35 U.S.C. 102. A further analysis would be necessary to determine if the process was unobvious under 35 U.S.C. 103.); Ex parte Novitski, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.).

Further, insofar as the instant claims rely on the preamble for setting for the intended use of the administration of a copper chelator or TTM, the preambles have not been given patentable weight. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). The only process steps of the instant claims are drawn to administering an amount of a copper chelator in an amount sufficient to inhibit IL-1α release, wherein the IL-1α release is non-traditional IL-1α release. It is understood that the claim preamble must be read in the context of the entire claim. The determination of whether preamble recitations are structural limitations or mere statements of purpose or use "can be resolved only on review of the entirety of the [record] to gain an understanding of what the inventors actually invented and intended to encompass by the claim." Corning Glass Works, 868 F.2d at 1257, 9 USPQ2d at 1966. If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also Rowe v. Dror, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir.1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation"); Kropa v. Robie, 187 F.2d at 152, 88 USPQ2d at 480-81 (preamble is not a limitation where claim is directed to a product and the preamble

merely recites a property inherent in an old product defined by the remainder of the claim); STX LLC. v. Brine, 211 F.3d 588, 591, 54 USPQ2d 1347, 1350 (Fed. Cir. 2000) (holding that the preamble phrase "which provides improved playing and handling characteristics" in a claim drawn to a head for a lacrosse stick was not a claim limitation). Compare Jansen v. Rexall Sundown, Inc., 342 F.3d 1329, 1333-34, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003) (In a claim directed to a method of treating or preventing pernicious anemia in humans by administering a certain vitamin preparation to "a human in need thereof," the court held that the preamble is not merely a statement of effect that may or may not be desired or appreciated, but rather is a statement of the intentional purpose for which the method must be performed. Thus the claim is properly interpreted to mean that the vitamin preparation must be administered to a human with a recognized need to treat or prevent pernicious anemia.); In re Cruciferous Sprout Litig., 301 F.3d 1343, 1346-48, 64 USPQ2d 1202, 1204-05 (Fed. Cir. 2002) (A claim at issue was directed to a method of preparing a food rich in glucosinolates wherein cruciferous sprouts are harvested prior to the 2-leaf stage. The court held that the preamble phrase "rich in glucosinolates" helps define the claimed invention, as evidenced by the specification and prosecution history, and thus is a limitation of the claim (although the claim was anticipated by prior art that produced sprouts inherently "rich in glucosinolates")). In the instant case, the preambles are in accord with at least Jansen v. Rexall Sundown, Inc., and In re Cruciferous Sprout Litig., because the preambles do not limit process steps of the claim. Instead, they merely explains the purpose of what a specific amount of a copper chelator is intended to do in various situations. In light of the facts and the law in this area, neither Brewer et al., nor Wempe et al., need not appreciate nor disclose the element of IL-1α release, a method of inhibiting IL-1α release from a cell, or the use of a copper chelator to inhibit IL-1α release from a cell in order to render the instant claims obvious.

Applicant argues that the test for obviousness has not been met (Remarks, p. 11, second paragraph). Applicant argues that there must be a suggestion in the references or the desirability of the combination (Remarks, p. 11, third paragraph). Applicant states that the deficiencies of Brewer have been discussed above (Remarks, p. 11, last paragraph). Applicant argues that Wempe does not teach a role for IL-1α in monocyte adhesion (Remarks, p. 13, second paragraph). Applicant argues that Wempe would not direct a skilled artisan to the present invention because Wempe teaches the importance of bFGF in MCP-1 expression and consequently suggests that bFGF is a mediator of inflammatory cell trafficking following balloon denudation injury (Remarks, p. 13, second paragraph). Applicant argues that because the mechanism of regulating MCP-1 expression by bFGF stimulation of endothelial cells as taught by Wempe does not predict or suggest the effect of IL-1α on macrophage infiltration or a method

of inhibiting IL-1α release from a cell or the like, the present invention cannot be obvious over Wempe alone. Applicant's arguments have been fully considered, but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With regard to Applicant's arguments regarding the strict construction and application of the TSM test, Applicant is directed to KSR v. Teleflex, Inc., 550 US at __, 82 USPQ2d 1385 (30 April 2007), which states, "[a]s our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." (KSR, at 1396). The Court continued, stating that "helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents." KSR, at 1390. The current and its analysis under 103(a) meets all of the *prima facie* requirements under Graham v. Deere (1966) (*supra*) and KSR v. Teleflex (2007) (*supra*).

With regard to the alleged deficiencies in Brewer, as set forth in detail above, the prior art need not appreciate an unknown property of the composition. When a claim recites using an old composition or structure and the use is directed to a result or property of that composition or structure, then the claim is anticipated. In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978). In the instant case, because WO 00/13712 teaches a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis (pages 3 and 55-56), by administering the copper chelator tetrathiomolybdate (pp. 19- 25), the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) has no bearing on patentability, particularly in light of the fact that Brewer et al., teaches administration of TTM to the same population and for the same overarching purpose, to treat mammals with vessel injury, inflammation, and arterial wall injury. Additionally, Brewer et al., also teaches administering TTM in the treatment of trauma, diabetic retinopathy, macular degeneration, vein occlusion, artery occlusion, chronic inflammatory diseases, and atherosclerosis at pp. 55-57; all of which are part of a blood vessel's response to injury and are involved in scar formation at the site of injury. Brewer et al., teaches the method of administering TTM for the same purpose claimed by Applicant, even

if the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) was unappreciated by Brewer et al.

With regard to Applicant's argument that Wempe does not teach a role for IL-1α in monocyte adhesion (Remarks, p. 13, second paragraph) and that Wempe would not direct a skilled artisan to the present invention because Wempe teaches the importance of bFGF in MCP-1 expression and consequently suggests that bFGF is a mediator of inflammatory cell trafficking following balloon denudation injury (Remarks, p. 13, second paragraph), Wempe et al., need not appreciate the involvement of IL-1α in recruiting macrophages/monocytes after vessel injury. This is appreciated in the prior art. See, for evidentiary purposes only, Issekutz (J Immunol, 1995 Jun 15;154(12):6533-40) (abstract; p. 6535, column 1, results; Figure 1) and Dayer et al., (cited as an evidentiary reference) provide evidence that cell-associated IL-1α plays a crucial role in the process of cell-cell interaction between monocytes and fibroblasts and that this interaction may be controlled by inhibitors of IL-1. It is sufficient that Wempe et al., teach the preferential adhesion of monocytic cells to migrating endothelial cells (including fibroblasts) demonstrated *in vivo* after balloon denudation injury of rat aortas (p. 5 of 16, second paragraph). One of ordinary skill in the art would understand the role played by IL-1α in the process of cell-cell interaction between monocytes and cell types such as fibroblasts (as evidenced by Dayer et al.,) and endothelial cells (as evidenced by Issekutz).

Conclusion

NO CLAIMS ARE ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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